

## **An Open-Label Randomized Trial of Intramuscular Olanzapine versus Oral Clonidine for Symptomatic Treatment of Opioid Withdrawal in the Emergency Department**

Original Protocol: October 1, 2015

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### **1.0 Objectives**

- 1.1* Purpose: The purpose of this study is to compare olanzapine versus clonidine in the treatment of symptoms of opioid withdrawal in the Emergency Department (ED).

### **2.0 Background**

- 2.1* Significance of Research Question/Purpose: Opioid withdrawal is a commonly encountered clinical scenario in the ED. Patients in opioid withdrawal present with symptoms including nausea, vomiting, diarrhea, abdominal pain, anxiety, agitation, among others. Treatment for opioid withdrawal generally falls into two broad categories; it can be treated with classes of non-opiate medications and opiate medications. There are certain environments, such as outpatient clinics that specialize in pain management and addiction, where the administration of opiates (methadone) or partial-opiate agonists (buprenorphine) may be the appropriate treatment for opioid withdrawal. The ED generally however does not have the resources to initiate these types of therapies, and the patients presenting to the emergency department are typically having a more acutely symptomatic withdrawal necessitating the need for non-opiate adjuncts to achieve rapid relief.
- 2.2* Preliminary Data: At this time, many ED physicians treat withdrawal with clonidine, which has been studied extensively [1]. Clonidine is an alpha-2 adrenergic agonist and is thought to blunt the symptoms of withdrawal by binding to central alpha-2 receptors. Other medications thought to be useful in opiate withdrawal include medications targeted at treating anxiety/agitation (benzodiazepines, diphenhydramine), anti-emetics (ondansetron, prochlorperazine), anti-diarrheals (loperamide), and non-narcotic pain medications (ibuprofen, acetaminophen). Although it has not been extensively studied, there is some literature to support that the use of atypical antipsychotics may be helpful in treatment of opiate withdrawal symptoms. These studies show that atypical antipsychotics may reduce opiate cravings, pain, and anxiety [2, 3] as well as gastrointestinal side effects [4]. Furthermore, we recently conducted a prospective evaluation

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of olanzapine in our ED and showed good efficacy in the treatment of nausea, vomiting, abdominal pain, and agitation, some of whom were in the ED for treatment of opioid withdrawal. We also conducted a large retrospective review of over 700 ED patients who received olanzapine for various clinical indications and found that olanzapine administration is very safe, with very low rates of airway complications, dystonia, and allergic reaction.

[1] Gowing L, Farrell MF, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev 2014 Mar 31;3:CD002024.

[2] Pinkofsky HB, Hahn AM, Campbell FA, Rueda J, Daley DC, Douaihy AB. Reduction of opioid-withdrawal symptoms with quetiapine. J Clin Psychiatry. 2005 Oct;66(10):1285-8

[3] Sarkar S, Mattoo SK. Newer approaches to opioid detoxification. Ind Psychiatry J. 2012 Jul;21(2):163-7. doi: 10.4103/0972-6748.119652.

[4] Mori T, Komiya S, Ohya J, Uzawa N, Sugiyama K, Saitoh Y, Shibasaki M, Suzuki T. Involvement of 5-HT<sub>2</sub> receptors in the expression of withdrawal diarrhea in morphine-dependent mice. Eur J Pharmacol. 2014 Oct 5;740:160-7.

### 3.0 Study Outcomes

3.1 Primary Outcome: The primary outcome is rescue sedation within 60 minutes of drug administration

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Rescue Medication: 60 minutes, 120 minutes, Time of Disposition

Clinical Opioid Withdrawal Scale: Baseline, 60 minutes, 120 minutes, Time of Disposition

OASS Score: Baseline, 60 minutes, 120 minutes, Time of Disposition

Adverse Events: Dystonia, Akathisia, Wheezing, Rash/Hives, Hypotension, Aspiration

Airway Events: Oxygen administration, Nasal/oral airway, Bag valve mask

Serious Adverse Events: Death, Intubation

### 4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: Study interventions will include:

(1) Randomization of initial treatment for symptoms of withdrawal to 0.3 mg of oral clonidine versus 10 mg of intramuscular olanzapine

- Intramuscular Olanzapine: FDA-approved medication and dose

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- Oral clonidine: FDA-approved medication and dose

4.2 Drug/Device Handling: This drug is being given open label. These drugs are routinely stored in the Department of Emergency Medicine Omnicell. There are no alterations to drug storage other than what is routine and standard of care for the Dept of Emergency Medicine. The drug will be administered or injected as it would be in routine clinical practice.

### 5.0 Procedures Involved

5.1 Study Design: Open label, unblinded, randomized clinical trial

5.2 Study Procedures:

After patients are consented and enrolled procedures are as follows:

- (1) Research Associate randomizes patient (random assignments will be placed in opaque envelopes and the next sequential envelope will be opened)
- (2) Research Associate will inform provider which medication the patient is randomized to
- (3) Provider will notify patient which medication they are randomized to and they will order the medication in the electronic medical record
- (4) Nurse will administer the medication to patient
- (5) Research Associate will perform baseline assessment (COWS score, OAAS score) & will obtain demographic information and opioid use history information from patient
- (6) No medications should be given to the patient for 30 minutes after administration of the initial medication; after 30 minutes any medication or treatment can be given to the patient as needed.
- (7) Research Associate will perform assessment 60 minutes, 120 minutes after medication administration and at the time of disposition (discharge or admission) including COWS score, OAAS score, and the names of additional treatments given by the ED provider during that interval.
- (8) Research Associate will record clinical information related to the counter including disposition, laboratory values, adverse events, serious adverse events, airway events, and time in department.
- (9) Note: all medication choices administered except for the initial randomized medication are at the discretion of the treating physician; there is no research protocol to dictate additional treatments

5.3 Study Duration: The study duration is from the time of enrollment to the time the patient is discharged or admitted to the hospital. The study duration does not extend past the patient's ED encounter.

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- 5.4 Individually Identifiable Health Information: Identifiable Health Information will be obtained including Medical Record Number. This number is necessary in order to access the patient's medical record. After this number is no longer needed, the database will be de-identified.

### 6.0 Sharing of Results with Participants

- 6.1 Results will not routinely shared with participants but the patient will have contact information including phone numbers to contact the investigators to answer any questions about study results if they query.,

### 7.0 Study Population

#### 7.1 Inclusion Criteria:

- Adult Patients (18 years of age and greater)
- Patients must be in the ED for symptoms that may be caused by opioid withdrawal
- The ED provider believes that medication treatment is indicated for the patient's symptoms opioid withdrawal

#### 7.2 Exclusion Criteria:

- Age < 18 years
- Inability to provide informed consent
- Allergy to either medication
- Prisoner/Under Arrest
- Known Pregnancy
- Already received treatment from their ED provider for symptoms

- 7.3 Screening: Patients will be screened by research associates and by ED providers for symptoms that could possibly be related to opioid withdrawal. An Opioid Use history may be elicited by the ED provider, or the patient may offer this history themselves. Screening will occur in the ED only.

### 8.0 Vulnerable Populations

- 8.1 Vulnerable Populations: No vulnerable populations will be approached for inclusion in this study. Patients in opioid withdrawal are healthy, and not impaired. By definition, they are not intoxicated.

### 9.0 Local Number of Participants

- 9.1 Local Number of Participants to be Consented: Up to 70

### 10.0 Local Recruitment Methods

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- 10.1* Recruitment Process: No external recruitment will occur, only patient's who are in the ED will be approached for possible enrollment
- 10.2* Identification of Potential Participants: Physicians will be actively searching for patients in the ED with symptoms of opioid withdrawal, and will be aware of this trial and will notify Research Associates if a patient may eligible to complete the screening process. Research Associates will also be screening patients in the ED that have chief complaints that may be related to opioid withdrawal (i.e. "nausea", "vomiting", "withdrawal") but this is not an inclusive list of chief complaints. Identification will rely almost exclusively on ED provider identification of appropriate patients.
- 10.3* Recruitment Materials: There are no recruitment materials.
- 10.4* Payment: There will be no payments

### 11.0 Withdrawal of Participants

- 11.1* Withdrawal Circumstances: Patients can withdraw at any time. They can withdraw as soon as consent as signed up until the study is closed. They can even choose to withdraw after data collection is complete, and are provided with a phone number to contact if that be the case.
- 11.2* Withdrawal Procedures: Patients must notify their doctor of the research associate to withdraw if they are in the ED still. If they are no longer in the ED they must call a phone number that is included in the consent form.
- 11.3* Termination Procedures: Data will not be used if the patient requests it not be used.

### 12.0 Risks to Participants

#### *12.1* Foreseeable Risks:

It is possible that enrolling in the study could slightly delay getting a medication for treatment of the patient's symptoms.

There is a possible risk of breach of data confidentiality but this will be mitigated by storing all forms in locked storage facilities and electronic databases are encrypted and password protected

Possible side effects of the two medications:

Olanzapine: drowsiness, extrapyramidal side effects, dizziness, headache, respiratory depression, hypotension, among others

Clonidine: drowsiness, headache, fatigue, abdominal pain, dry mouth, hypotension, among others

Of note, these medications are also used frequently in the ED, so it is likely that either or both of these medications would be given as part of routine clinical care.

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*12.2* Reproduction Risks: A known pregnancy will also be an exclusion criteria. We will not require a urine pregnancy test but one may be obtained at the discretion of the ED provider, as in many cases this will be part of usual care. Both study medications administered are considered pregnancy category C and are frequently used in the pregnant population as a standard of care.

*12.3* Risks to Others: N/A

### 13.0 Potential Benefits to Participants

*13.1* Potential Benefits There is no direct benefit to the patient for being in this study

### 14.0 Statistical Considerations

*14.1* Data Analysis Plan: Demographic data will be described using descriptive statistics, including means, medians, and proportions as appropriate. The primary outcome will be the rate of rescue medication given within 60 minutes. This will be calculated as a proportion. The comparison of the primary outcome will be a calculation of the difference in proportions with associated 95% confidence intervals. A difference in proportions with associated 95% confidence intervals will also be calculated for secondary outcomes including rescue medication at 120 minutes and during the entire encounter. Adverse events will be reported as counts and proportions.

*14.2* Power Analysis: Sample size calculations were performed using estimates from a previous study looking at patients who received olanzapine in the ED for all indications. A subset of these patients received the olanzapine for opioid withdrawal and approximately 40% of those patients received rescue medications. We estimated that olanzapine would result in a relative reduction of rescue medication administration of 50% compared to clonidine. We would therefore need at least 56-70 patients total to achieve 80%-90% power, respectively, with a two-sided alpha of 0.05.

*14.3* Data Integrity: Standardized data collection forms will be used to ensure data integrity. After a patient is enrolled and data is collected, a trained research coordinator will review the data collection forms. They will attempt to complete any missing data points using the patients' medical record and via query of the patients treating physician if appropriate. The principal investigator will also review the database on a rolling (at least monthly) basis to ensure that data collection is complete. An interim data analysis will be performed.

### 15.0 Confidentiality

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*15.1* Data Security: Data will be stored on a password protected encrypted database that only the investigators and research coordinators have access to. Paper data collection forms are stored in a locked facility.

### 16.0 Provisions to Monitor the Data to Ensure the Safety of Participants

All serious adverse events will be reviewed immediately by the investigators and reported the next business day IRB. All serious adverse events will also be reviewed by the listed Co-Investigators and the Research Director (this group will serve as a Data Safety Monitoring Board) to determine the extent to which it was related to the study drug and assess appropriateness of continuing the trial on a case-by-case basis. All other non-serious adverse events will be reported on the annual report.

An interim analysis will occur after the first 40 patients are enrolled by the lead investigator and will be presented to the listed Co-Investigators and the Research Director (this group will serve as a Data Safety Monitoring Board). Efficacy outcomes will be assessed, and safety outcomes will be assessed. If there are significant disparate safety concerns, then the study will be terminated. Significant safety concerns are defined as a rate of serious adverse events (mortality, intubation) that is significantly greater in one group than the other.

Furthermore, a yearly continuing review form will be submitted by the investigators to the IRB.

### 17.0 Provisions to Protect the Privacy Interests of Participants

*17.1* Protecting Privacy: Data will be stored on a password protected encrypted database that only the investigators and research coordinators have access to. Paper data collection forms are stored in a locked facility.

### 18.0 Consent Process

*18.1* Consent Process (when consent will be obtained): Informed consent from the patient must be obtained for every patient or from their legally authorized representative. There will be no alterations in consent accepted for this trial. Consent will be obtained after the patient has been confirmed eligible. Consent will be obtained by the treating ED provider.